

CLAIMS

1. An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for an epitope of CD38 (SEQ ID NO: 22), wherein said antibody or functional fragment thereof is able to mediate killing of a CD38+ target cell by ADCC with an at least five-fold better efficacy than chimeric OKT10 (SEQ ID NOS: 23 and 24) under the same or substantially the same conditions when a human PBMC cell is employed as an effector cell, wherein said CD38+ target cell is selected from the group consisting of LP-1 (DSMZ: ACC41) and RPMI-8226 (ATCC: CCL-155), and wherein the ratio of effector cells to target cells is between about 30:1 and about 50:1.
2. An isolated antigen-binding region of an antibody or functional fragment thereof according to claim 1.
3. An isolated antigen-binding region according to claim 2, which comprises an H-CDR3 region depicted in SEQ ID NO: 5, 6, 7, or 8.
4. An isolated antigen-binding region according to claim 3, further comprising an H-CDR2 region depicted in SEQ ID NO: 5, 6, 7, or 8.
5. An isolated antigen-binding region according to claim 4, further comprising an H-CDR1 region depicted in SEQ ID NO: 5, 6, 7, or 8.
6. An isolated antigen-binding region according to claim 5, which comprises a variable heavy chain depicted in SEQ ID NO: 5, 6, 7, or 8.
7. An isolated antigen-binding region according to claim 2, which comprises an L-CDR3 region depicted in SEQ ID NO: 13, 14, 15, or 16.
8. An isolated antigen-binding region according to claim 7, further comprising an L-CDR1 region depicted in SEQ ID NO: 13, 14, 15, or 16.

9. An isolated antigen-binding region according to claim 8, further comprising an L-CDR2 region depicted in SEQ ID NO: 13, 14, 15, or 16.
10. An isolated antigen-binding region according to claim 9, which comprises a variable light chain depicted in SEQ ID NO: 13, 14, 15, or 16.
11. An isolated antigen-binding region according to claim 2, which comprises a heavy chain amino acid sequence selected from the group consisting of (i) SEQ ID NO: 5, 6, 7, or 8; and (ii) a sequence having at least 60 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NO: 5, 6, 7, or 8.
12. An isolated antigen-binding region according to claim 2, which comprises a light chain amino acid sequence selected from the group consisting of (i) SEQ ID NO: 13, 14, 15, or 16; and (ii) a sequence having at least 60 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NO: 13, 14, 15, or 16.
13. An isolated antibody to according to claim 1, which is an IgG.
14. An isolated antibody to according to claim 13, which is an IgG1.
15. An isolated human or humanized antibody or functional fragment thereof, comprising an antigen-binding region that is specific for an epitope of CD38 (SEQ ID NO: 22), wherein said antibody or functional fragment thereof is able to mediate killing of a CD38-transfected CHO cell by CDC with an at least two-fold better efficacy than chimeric OKT10 (SEQ ID NOS: 23 and 24) under the same or substantially the same conditions.
16. An isolated antigen-binding region of an antibody or functional fragment thereof according to claim 15.

17. An isolated antigen-binding region according to claim 16, which comprises an H-CDR3 region depicted in SEQ ID NO: 5, 6, or 7.
18. An isolated antigen-binding region according to claim 17, further comprising an H-CDR2 region depicted in SEQ ID NO: 5, 6, or 7.
19. An isolated antigen-binding region according to claim 18, further comprising an H-CDR1 region depicted in SEQ ID NO: 5, 6, or 7.
20. An isolated antigen-binding region according to claim 19, which comprises a variable heavy chain depicted in SEQ ID NO: 5, 6, or 7.
21. An isolated antigen-binding region according to claim 16, which comprises an L-CDR3 region depicted in SEQ ID NO: 13, 14, or 15.
22. An isolated antigen-binding region according to claim 21, further comprising an L-CDR1 region depicted in SEQ ID NO: 13, 14, or 15.
23. An isolated antigen-binding region according to claim 22, further comprising an L-CDR2 region depicted in SEQ ID NO: 13, 14, or 15.
24. An isolated antigen-binding region according to claim 23, which comprises a variable light chain depicted in SEQ ID NO: 13, 14, or 15.
25. An isolated antigen-binding region according to claim 16, which comprises a heavy chain amino acid sequence selected from the group consisting of (i) SEQ ID NO: 5, 6, or 7; and (ii) a sequence having at least 60 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NO: 5, 6, or 7.
26. An isolated antigen-binding region according to claim 16, which comprises a light chain amino acid sequence selected from the group consisting of (i) SEQ ID NO: 13, 14, or 15; and (ii) a sequence having at least 60 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NO: 13, 14, or 15.

27. An isolated antibody to according to claims 15, which is an IgG.
28. An isolated antibody to according to claim 27, which is an IgG1.
29. An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for an epitope of CD38, wherein the epitope comprises one or more amino acid residues of amino acid residues 1 to 215 of CD38 (SEQ ID NO: 22).
30. An isolated antibody or functional fragment thereof of claim 29, wherein the epitope comprises one or more amino acid residues comprised in one or more of the amino acid stretches taken from the list of amino acid stretches 44-66, 82-94, 142-154, 148-164, 158-170, and 192-206 of CD38.
31. An isolated antibody or functional fragment thereof according to claim 29, wherein said epitope is a linear epitope.
32. An isolated antibody or functional fragment thereof according to claim 31, wherein said antigen-binding region comprises an H-CDR3 region depicted in SEQ ID NO: 6.
33. An isolated antibody or functional fragment thereof according to claim 32, wherein said antigen-binding region further comprises an H-CDR2 region depicted in SEQ ID NO: 6.
34. An isolated antibody or functional fragment thereof according to claim 33, wherein said antigen-binding region further comprises an H-CDR1 region depicted in SEQ ID NO: 6.
35. An isolated antibody or functional fragment thereof according to claim 31, which comprises a variable heavy chain depicted in SEQ ID NO: 6.

36. An isolated antibody or functional fragment thereof according to claim 31, wherein said antigen-binding region comprises an L-CDR3 region depicted in SEQ ID NO: 14.
37. An isolated antibody or functional fragment thereof according to claim 36, wherein said antigen-binding region further comprises an L-CDR1 region depicted in SEQ ID NO: 14.
38. An isolated antibody or functional fragment thereof according to claim 37, wherein said antigen-binding region further comprises an L-CDR2 region depicted in SEQ ID NO: 14.
39. An isolated antibody or functional fragment thereof according to claim 31, which comprises a variable light chain depicted in SEQ ID NO: 14.
40. An isolated antibody or functional fragment thereof according to claim 31, which comprises a heavy chain amino acid sequence selected from the group consisting of (i) SEQ ID NO: 6; and (ii) a sequence having at least 60 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NO: 6.
41. An isolated antibody or functional fragment thereof according to claim 31, which comprises a light chain amino acid sequence selected from the group consisting of (i) SEQ ID NO: 14; and (ii) a sequence having at least 60 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NO: 14.
42. An isolated functional fragment according to claim 31, which is a Fab or scFv antibody fragment.
43. An isolated antibody according to claim 31, which is an IgG.
44. An isolated antibody according to claim 43, which is an IgG1.

45. An isolated antibody or functional fragment thereof according to claim 29, wherein said epitope is a conformational epitope.
46. An isolated antibody or functional fragment thereof according to claim 45, wherein said antigen-binding region comprises an H-CDR3 region depicted in SEQ ID NO: 5, 7, or 8.
47. An isolated antibody or functional fragment thereof according to claim 46, wherein said antigen-binding region further comprises an H-CDR2 region depicted in SEQ ID NO: 5, 7, or 8.
48. An isolated antibody or functional fragment thereof according to claim 47, wherein said antigen-binding region further comprises an H-CDR1 region depicted in SEQ ID NO: 5, 7, or 8.
49. An isolated antibody or functional fragment thereof according to claim 45, which comprises a variable heavy chain depicted in SEQ ID NO: 5, 7, or 8.
50. An isolated antibody or functional fragment thereof according to claim 45, wherein said antigen-binding region comprises an L-CDR3 region depicted in SEQ ID NO: 13, 15, or 16.
51. An isolated antibody or functional fragment thereof according to claim 50, wherein said antigen-binding region further comprises an L-CDR1 region depicted in SEQ ID NO: 13, 15, or 16.
52. An isolated antibody or functional fragment thereof according to claim 51, wherein said antigen-binding region further comprises an L-CDR2 region depicted in SEQ ID NO: 13, 15, or 16.
53. An isolated antibody or functional fragment thereof according to claim 45, which comprises a variable light chain depicted in SEQ ID NO: 13, 15, or 16.

54. An isolated antibody or functional fragment thereof according to claim 45, which comprises a heavy chain amino acid sequence selected from the group consisting of (i) SEQ ID NO: 5, 7, or 8; and (ii) a sequence having at least 60 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NO: 5, 7, or 8.
55. An isolated antibody or functional fragment thereof according to claim 45, which comprises a light chain amino acid sequence selected from the group consisting of (i) SEQ ID NO: 13, 15, or 16; and (ii) a sequence having at least 60 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NO: 13, 15, or 16.
56. An isolated functional fragment according to claim 45, which is a Fab or scFv antibody fragment.
57. An isolated antibody according to claim 45, which is an IgG.
58. An isolated antibody according to claim 57, which is an IgG1.
59. A variable heavy chain of an isolated antibody or functional fragment thereof that is encoded by (i) a nucleic acid sequence comprising SEQ ID NO: 1, 2, 3, or 4, or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 1, 2, 3, or 4, wherein said antibody or functional fragment thereof is specific for an epitope of CD38.
60. A variable light chain of an isolated antibody or functional fragment thereof that is encoded by (i) a nucleic acid sequence comprising SEQ ID NO: 9, 10, 11, or 12, or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 9, 10, 11, or 12, wherein said antibody or functional fragment thereof is specific for an epitope of CD38.

61. An isolated nucleic acid sequence that encodes an antigen-binding region of a human antibody or functional fragment thereof that is specific for an epitope of CD38.
62. A nucleic acid sequence encoding a variable heavy chain of an isolated antibody or functional fragment thereof, which comprises (i) a sequence selected from the group consisting of SEQ ID NOS: 1, 2, 3 and 4 or (ii) a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 1, 2, 3 or 4, wherein said antibody or functional fragment thereof is specific for an epitope of CD38.
63. A nucleic acid sequence encoding a variable light chain of an isolated antibody or functional fragment thereof, which comprises (i) a sequence selected from the group consisting of SEQ ID NOS: 9, 10, 11 and 12 or (ii) a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 9, 10, 11 or 12, wherein said antibody or functional fragment thereof is specific for an epitope of CD38.
64. A vector comprising a nucleic acid sequence according to any one of claims 61-63.
65. An isolated cell comprising a vector according to claim 64.
66. An isolated cell according to claim 65, wherein said cell is bacterial.
67. An isolated cell according to claim 65, wherein said cell is mammalian.
68. A pharmaceutical composition comprising an antibody or functional fragment according to any one of claims 1, 15 and 29 and a pharmaceutically acceptable carrier or excipient therefor.

69. A method for treating a disorder or condition associated with the undesired presence of CD38+ cells, comprising administering to a subject in need thereof an effective amount of the pharmaceutical composition according to claim 68.
70. A method according to claim 69, wherein said disorder or condition is a haematological disease.
71. A method according to claim 70 taken from the list of multiple myeloma, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, and acute lymphocytic leukemia.
72. A method according to claim 69, wherein said disorder or condition is an inflammatory disease
73. A method according to claim 72 taken from the list of rheumatoid arthritis and systemic lupus erythematosus.
74. A method for targeting CD38+ cells in a subject or a cell sample, comprising the step of allowing said CD38+ cells to be contacted with an antibody or functional fragment thereof according to any one of claims 1, 15 and 29.
75. A method of using an epitope of CD38 for isolating a human or humanized antibody or functional fragment thereof, wherein said antibody or functional fragment thereof comprises an antigen-binding region that is specific for said epitope, and wherein said method comprises the steps of:
 - a) contacting said epitope of CD38 with an antibody library; and
 - b) isolating said antibody or functional fragment thereof,wherein said epitope is a linear epitope.
76. A method according to claim 75, wherein said linear epitope comprises amino acid residues 192-206.

77. A method of using an epitope of CD38 for isolating a human or humanized antibody or functional fragment thereof, wherein said antibody or functional fragment thereof comprises an antigen-binding region that is specific for said epitope, and wherein said method comprises the steps of:
 - a) contacting said epitope of CD38 with an antibody library; and
 - b) isolating said antibody or functional fragment thereof,
wherein said epitope is a conformational epitope.
78. A method according to claim 77, wherein said conformational epitope comprises one or more amino acid sequences selected from the group consisting of amino acids 44-66, 82-94, 142-154, 148-164, 158-170, and 202-224 of CD38.
79. An isolated epitope of CD38 consisting essentially of an amino acid sequence selected from the group consisting of amino acids 44-66, 82-94, 142-154, 148-164, 158-170, 192-206 and 202-224 of CD38..
80. An isolated epitope of CD38 consisting of an amino acid sequence selected from the group consisting of amino acids 44-66, 82-94, 142-154, 148-164, 158-170, 192-206 and 202-224 of CD38.
81. A kit comprising an isolated epitope of CD38 comprising one or more amino acid stretches taken from the list of 44-66, 82-94, 142-154, 148-164, 158-170, 192-206 and 202-224 and an antibody library and instructions for use.
82. A human antibody according to any one of claims 1, 15 and 29, wherein the human antibody is a synthetic human antibody.
83. An isolated antigen-binding region according to any one of claims 11, 12, 25 and 26, wherein said sequence identity is at least 80%.

84. An isolated antibody or functional fragment thereof according to any one of claims 40, 41, 54 and 55, wherein said sequence identity is at least 80%.